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Application No.: 10/560,501

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Docket No.: WIBL-P01-013

AMENDMENTS TO THE CLAIMS

1. **(Original)** A method of modulating a biological response in a cell, the method comprising contacting the cell with at least one agent that modulates the expression or activity of $\text{Err}\alpha$ or Gabp , wherein the biological response is
 - (a) expression of at least one OXPHOS gene;
 - (b) mitochondrial biogenesis;
 - (c) expression of Nuclear Respiratory Factor 1 (NRF-1);
 - (d) β -oxidation of fatty acids;
 - (e) total mitochondrial respiration;
 - (f) uncoupled respiration;
 - (g) mitochondrial DNA replication;
 - (h) expression of mitochondrial enzymes; or
 - (i) skeletal muscle fiber-type switching.
2. **(Original)** The method of claim 1, wherein the agent increases at least one of the biological responses.
3. **(Original)** The method of claim 1, wherein the agent modulates the formation of a complex between a PGC-1 polypeptide and (i) an $\text{Err}\alpha$ polypeptide; or (ii) a Gabp polypeptide.
- 4-5. **(Canceled)**
6. **(Original)** The method of claim 1, wherein the agent modulates the expression level or the transcriptional activity of an $\text{Err}\alpha$ polypeptide, a Gabp polypeptide, or of both.
- 7-10. **(Canceled)**
11. **(Original)** The method of claim 1, wherein the cell is in an organism.

Application No.: 10/560,501

Docket No.: WIBL-P01-013

12. **(Previously Presented)** The method of claim 11, wherein the organism is a mammal.
13. **(Previously Presented)** The method of claim 12, wherein the mammal is a human.
14. **(Previously Presented)** The method of claim 13, wherein the human is afflicted with a disorder characterized by reduced mitochondrial activity.
15. **(Previously Presented)** The method of claim 14, wherein the disorder is diabetes, obesity, cardiac myopathy, aging, coronary atherosclerotic heart disease, diabetes mellitus, Alzheimer's Disease, Parkinson's Disease, Huntington's disease, dystonia, Leber's hereditary optic neuropathy (LHON), schizophrenia, myodegenerative disorders such as "mitochondrial encephalopathy, lactic acidosis, and stroke" (MELAS), and "myoclonic epilepsy ragged red fiber syndrome" (MERRF), NARP (Neuropathy; Ataxia; Retinitis Pigmentosa), MNGIE (Myopathy and external ophthalmoplegia, neuropathy; gastro-intestinal encephalopathy, Kearns-Sayre disease, Pearson's Syndrome, PEO (Progressive External Ophthalmoplegia), congenital muscular dystrophy with mitochondrial structural abnormalities, Wolfram syndrome, Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy Deafness, Leigh's Syndrome, fatal infantile myopathy with severe mitochondrial DNA (mtDNA) depletion, benign "later-onset" myopathy with moderate reduction in mtDNA, dystonia, medium chain acyl-CoA dehydrogenase deficiency, arthritis, mitochondrial diabetes and deafness (MIDD), or mitochondrial DNA depletion syndrome.
16. **(Canceled)**
17. **(Original)** A method of determining if an agent is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function, the method comprising determining if the agent increases:
 - (i) the expression or activity of $\text{Err}\alpha$ or Gapb in a cell; or

Application No.: 10/560,501

Docket No.: WIBL-P01-013

(ii) the formation of a complex between a PGC-1 polypeptide and (i) an $\text{Err}\alpha$ polypeptide; or (ii) a Gabp polypeptide;
wherein an agent that increases (i) or (ii) is a potential target for the treatment of the disorder.

18. (Canceled)

19. (Previously Presented) The method of claim 17, wherein the agent increases the formation of the complex, and wherein the agent increases the biological response.

20. (Original) The method of claim 19, wherein the agent decreases the formation of the complex, and wherein the agent decreases the biological response.

21. (Canceled)

22-34. (Canceled)

35. (Original) A method of reducing the metabolic rate of a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an agent which decreases the expression or activity of at least one of the following:

(i) $\text{Err}\alpha$;

(ii) Gabpa;

(iii) a gene having an $\text{Err}\alpha$ binding site, a Gabpa binding site, or both; or(iv) a transcriptional activator which binds to an $\text{Err}\alpha$ binding site or to a Gabpa binding site;

thereby reducing the metabolic rate of the patient.

36-41. (Canceled)

Application No.: 10/560,501

Docket No.: WIBL-P01-013

42. **(Original)** A method of identifying a susceptibility locus for a disorder that is characterized by reduced mitochondrial function, glucose intolerance, or insulin intolerance in a subject, the method comprising

(i) identifying at least one polymorphisms in a gene, or linked to a gene, wherein the gene (a) has an $\text{Err}\alpha$ binding site, a Gabpa binding site, or both; or (b) is $\text{Err}\alpha$, Gabpa , or Gabpb ;

(ii) determining if at least one polymorphism is associated with the incidence of the disorder,

wherein if a polymorphism is associated with the incidence of the disorder then the gene having the polymorphism, or the gene to which the polymorphism is linked, is a susceptibility locus.

43-46. **(Canceled)**

47. **(Previously Presented)** A method of determining if a subject is at risk of developing a disorder which is characterized by reduced mitochondrial function, the method comprising determining if a gene from the subject contains a mutation which reduces the function of the gene, wherein the gene has an $\text{Err}\alpha$ binding site, a Gapba binding site, or both, wherein if a gene from the subject contains the mutation then the subject is at risk of developing the disorder.

48-77. **(Canceled)**

78. **(Original)** A method of detecting statistically-significant differences in the expression level of at least one biomarker belonging to a biomarker set, between the members of a first and of a second experimental group, comprising:

(a) obtaining a biomarker sample from members of the first and the second experimental groups;

Application No.: 10/560,501

Docket No.: WIBL-P01-013

- (b) determining, for each biomarker sample, the expression levels of at least one biomarker belonging to the biomarker set and of at least one biomarker not belonging to the set;
- (c) generating a rank order of each biomarker according to a difference metric of its expression level in the first experimental group compared to the second experimental group;
- (d) calculating an experimental enrichment score for the biomarker set by applying a non parametric statistic; and
- (e) comparing the experimental enrichment score with a distribution of randomized enrichment scores to calculate the fraction of randomized enrichment scores greater than the experimental enrichment score, wherein a low fraction indicates a statistically-significant difference in the expression level of the biomarker set between the members of the first and of the second experimental group.

79-92. (Canceled)

93. (Original) A method of identifying an agent that regulates expression of OXPHOS-CR genes, the method comprising

- (a) contacting (i) an agent to be assessed for its ability to regulate expression of OXPHOS-CR genes with (ii) a test cell; and
- (b) determining whether the expression of at least two OXPHOS-CR gene products show a coordinate change in the test cell compared to an appropriate control, wherein a coordinate change in the expression of the OXPHOS-CR gene products indicates that the agent regulates the expression of OXPHOS-CR genes.

94-105. (Canceled)

Application No.: 10/560,501

Docket No.: WIBL-P01-013

106. (New) The method of claim 93, wherein a coordinate change in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential modulator of the expression or activity of $\text{Err}\alpha$ or Gabp .
107. (New) The method of claim 106, wherein a coordinate change in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential agent for modulating mitochondrial biogenesis, expression of Nuclear Respiratory Factor 1 (NRF-1), β -oxidation of fatty acids, total mitochondrial respiration, uncoupled respiration, mitochondrial DNA replication, expression of mitochondrial enzymes, or skeletal muscle fiber-type switching.
108. (New) The method of claim 93, wherein the method comprises determining whether the expression of at least two OXPHOS-CR gene products show a coordinate increase in the test cell as compared to an appropriate control.
109. (New) The method of claim 108, wherein a coordinate increase in the expression of the OXPHOS-CR gene products indicates that the agent is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.
110. (New) The method of claim 108, wherein a coordinate increase in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential agent for increasing expression or activity of $\text{Err}\alpha$ or Gabp .
111. (New) The method of claim 110, wherein an agent that increases expression or activity of $\text{Err}\alpha$ or Gabp is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.

Application No.: 10/560,501

Docket No.: WIBL-P01-013

112. (New) The method of claim 110, wherein a coordinate increase in the expression of the OXPHOS-CR gene products indicates that the agent is a potential agent for increasing mitochondrial biogenesis, expression of Nuclear Respiratory Factor 1 (NRF-1), β -oxidation of fatty acids, total mitochondrial respiration, uncoupled respiration, mitochondrial DNA replication, expression of mitochondrial enzymes, or skeletal muscle fiber-type switching.
113. (New) The method of claim 93, further comprising assessing the effect of the agent on mitochondrial number or on a mitochondrial function.
114. (New) The method of claim 93, further comprising assessing whether the agent increases a desired biological response that is impaired in subjects having a disorder that is characterized by glucose intolerance, insulin resistance, or decreased mitochondrial function.
115. (New) The method of claim 93, further comprising administering the agent to a mammalian organism.
116. (New) The method of claim 115, wherein the mammalian organism is human.
117. (New) The method of claim 115, wherein the mammalian organism is a test animal that serves as a model for a disorder characterized by glucose intolerance, insulin resistance, or decreased mitochondrial function.